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DBU-mediated transformation of arylmethylenecyclopropenes to alkylidenecyclopropanes

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Methylenecyclopropanes or alkylidenecyclopropanes (MCPs or ACPs) are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.¹ MCPs (ACPs) can undergo a variety of ring-opening reactions because the release of the cyclopropyl ring strain (40 kcal/mol)² can provide a thermodynamic driving force and the π -character of the ring bonds of the cyclopropane can afford the kinetic opportunity to initiate the unleashing of the strain.³ Since the 1970s, the chemistry of MCPs (ACPs) has been widely explored in the presence of transition metal catalysts⁴ and the developments in this field have been comprehensively reviewed by Binger and Buech,⁵ Donaldson,⁶ Lautens et al.,⁷ Yamamoto and co-workers,⁸ Shi et al.,⁹ Rubin et al.,¹⁰ Scheme 1 shows one of the most popular methods for the synthesis of MCPs (ACPs), in which a two-step process is involved including the formation of 3-bromo-triphenvlphosphonium bromide from the reaction of 1.3-dibromopropane with triphenylphosphine and a subsequent Wittig reaction with ketones and aldehydes.¹¹

Another useful preparation method is the Rh(I)-catalyzed [2+1] cyclopropanation of allenes with dizaocompounds (Scheme 2).¹² In this Letter, we wish to report an alternative method for the preparation of ACPs in moderate to good yields with good stereoselectivities in most cases under mild conditions from a DBU-mediated isomerization of arylmethylenecyclopropenes (Scheme 2).

Initially, we started to prepare various cyclopropenes **1** by means of Rh-catalyzed cyclopropanation of alkynes with diazo

ABSTRACT

An interesting DBU-mediated intramolecular isomerization of arylmethylenecyclopropenes **1** to alkylidenecyclopropanes (ACPs) has been described in this context. A variety of ACPs were obtained through a base-assisted manner in moderate to good yields under mild conditions with good stereoselectivities in most cases.

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Scheme 1. One of the most popular methods for the synthesis of MCPs (ACPs).



Scheme 2. Alternative methods for the preparation of alkylidenecyclopropanes (ACPs).

compounds **2**. During the optimization of the reaction conditions (see Supplementary data), we found that Rh_2esp_2 (bis[rhodium ($\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid)]) is the best catalyst for this transformation, affording the corresponding cycloadducts **3** in good yields in toluene at room temperature (Table 1).





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Table 1

Preparation of various cyclopropenes 3



^a Standard reaction conditions: **2** (1.5 mmol, 3.0 equiv) in a degassed toluene (15 mL) was added to a 5 mL toluene solution of **1** (0.5 mmol, 1.0 equiv) and Rh₂esp₂ (0.5 mol %) by a micro-injection pump within 10 h at room temperature under argon, and then, the reaction mixtures were stirred at room temperature for 4 h under argon.

^b Isolated samples.

With these cyclopropenes in hand, the base-promoted isomerization has been examined using 3a as a model substrate with a variety of bases including inorganic bases and the results are shown in Table 2. Using HMPA (hexamethylphosphoramide) (1.0 equiv) as a base promoter afforded ACP 4a in 72% yield in THF within 5 h (Table 2, entry 1). Increasing the employed amounts of HMPA to 2.0, 3.0, or 4.0 equiv provided 4a in 80% or 85% yields, respectively (Table 2, entries 2-4). Using a strong base such as LDA afforded 4a in 60% yield (Table 2, entry 5). The examination of other organic bases (3.0 equiv) such as Et₃N, DMAP (4-N,N-dimethylaminopyridine) and DBU (1,8-diazabicyclo[5.4.0] undec-7-ene) revealed that DBU is the most efficient base promoter in this reaction, affording 4a in 92% yield in THF (Table 2, entries 6-8). Inorganic bases are not effective promoters in this reaction (Table 2, entries 9-11). We also examined the solvent effects in this reaction and found that THF is the solvent of choice, giving 4a in higher yield (Table 2, entries 12-16).

Under the optimized conditions, we next investigated the substrate tolerance of this DBU promoted isomerization of strained small ring and the results are summarized in Table 3. As can be seen from Table 3, arylmethylenecyclopropenes **3b** and **3c** afforded

Table 2 Optimization of the reaction conditions for base-promoted isomerization of 3a

| $\begin{array}{c} CO_2Et \\ \hline \\ CF_3 \\ \hline \\ 3a \end{array} \begin{array}{c} base \\ \hline \\ solvent, temp \end{array} \begin{array}{c} CO_2Et \\ \hline \\ \\ 4a \end{array}$ | | | | | D₂Et ≿F₃ |
|---|--------------------------------|---------|---------|-----------|------------------------|
| Entry ^a | Base | 3a:base | Solvent | Temp (°C) | Yield ^b (%) |
| 1 | HMPA | 1:1 | THF | rt | 72 |
| 2 | HMPA | 1:2 | THF | rt | 80 |
| 3 | HMPA | 1:3 | THF | rt | 85 |
| 4 | HMPA | 1:4 | THF | rt | 85 |
| 5 | LDA | 1:3 | THF | rt | 60 |
| 6 | Et ₃ N | 1:3 | THF | rt | 41 |
| 7 | DMAP | 1:3 | THF | rt | 56 |
| 8 | DBU | 1:3 | THF | rt | 92 |
| 9 | NaOH | 1:3 | THF | rt | 14 |
| 10 | Na_2CO_3 | 1:3 | THF | rt | _ |
| 11 | K ₂ CO ₃ | 1:3 | THF | rt | _ |
| 12 | DBU | 1:3 | DCM | rt | 88 |
| 13 | DBU | 1:3 | Toluene | rt | 76 |
| 14 | DBU | 1:3 | DMF | rt | 80 |
| 15 | DBU | 1:3 | DCE | rt | 87 |
| 16 | DBU | 1:3 | THF | 60 | 92 |

^a The reactions were carried out with cycloprene **3a** (0.2 mmol, 1 equiv) and base (\times equiv) in 2 mL solvent at room temperature within 5 h under argon. ^b Isolated yields.

the desired ACPs 4b and 4c in 89% and 65% yields under the standard conditions, respectively (Table 3, entries 2 and 3). However, using **3d** as the substrate, no reaction occurred, suggesting that an arylmethylene group is required for this base promoted isomerization (Table 3, entry 4). Moreover, regardless of whether Ar is a naphthyl group or Ar bearing an electron-rich or -poor group, the reactions proceeded smoothly to give the corresponding products 4e-4i in good yields, indicating that the electronic property of the Ar group did not have significant impact on the reaction outcomes (Table 3, entries 5-9). Other substrates, such as 3j and 3l in which $R^1 = R^2 = F$ or $R^1 = H$, $R^2 = CF_3$, respectively, also afforded the desired products 4j and 4l in good yields under the standard conditions (Table 3, entries 10 and 12). Using arylmethylenecyclopropenone **3k** as the substrate, no desired product was formed and complex product mixtures were obtained (Table 3, entry 11). It should be also noted that in most cases, the desired ACPs were formed as only E-configuration or E:Z ratio = 98:2 (entry 3). Only in the case of 3j, the corresponding ACP 4j was formed in a E:Z ratio = 1:0.9, perhaps due to the electronic property of fluorine atom (Table 3, entry 10).

The further transformations of **4a** have been indicated in Schemes 3 and 4, respectively. The hydroxylation of the ester group in **4a** produced **5a** in 91% yield, which could be used to react with *p*-bromobenzylamine in the presence of EDCI and HOBt to give the corresponding amide product **6a** in 45% yield (Scheme 3). The structure of **5a** has been assigned by X-ray diffraction. The ORTEP drawing is shown in Figure 1 and the CIF data are presented in the Supplementary data.¹³

Upon treating ACP **4a** with *N*-iodosuccinimide (NIS) in CH_3CN : H_2O , a highly stereoselective iodolactonization took place to give **5b** in 64% yield (Scheme 4).^{12a}

To verify the reaction pathway, the isotope labeling experiment has been performed upon treating **3a–d** (see Supplementary data) under the standard conditions and the desired product **4a**–d was obtained in 92% yield with one deuterium (100% D) incorporated at the cyclopropyl ring, supporting the hydrogen transferred from benzylic position to the cyclopropyl ring in product **4** (Scheme 5).

Based on the above investigations, we proposed a plausible reaction mechanism for this DBU-promoted isomerization in Scheme 6. Deprotonation of **3** with DBU gives intermediate **A**, which undergoes an allylic migration to give intermediate **B**.

Table 3

The substrate scope of base-promoted isomerization of cyclopropenes



^a Standard reaction conditions: **3** (0.2 mmol, 1 equiv) and DBU (0.6 mmol, 3 equiv) were stirred in 2 mL THF at room temperature within 5 h under argon.

^b Isolated yields. n.r. = no reaction, n.p. = no desired product.

Reprotonation of intermediate **B** with DBU-H⁺ affords the desired product **4**.

In conclusion, we have developed an interesting organic basepromoted isomerization of a variety of arylmethylenecyclopropenes to alkylidenecyclopropane under mild conditions, affording the desired ACPs in good yields with good stereoselectivities in most cases. As for other type of cyclopropenes, Vidal reported a similar double-bond migration process to prepare alkylidenecyclopropanes under harsh conditions and the desired products were obtained in low E/Z selectivity (typical case, E: Z = 7:3).¹⁴ Further



Scheme 3. The further transformation of 4a by hydroxylation.



Scheme 4. The further transformation of 4a by the reaction with NIS.







Scheme 5. Deuterium labeling experiments



Scheme 6. A plausible reaction mechanism.

investigation on the mechanistic insights and the extension of this procedure to the synthesis of other types of ACPs in high stereoselectivity is under way in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013. 04.076.

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- 13. The crystal data of **5a** have been deposited in CCDC with number 918658. Empirical formula: $C_{12}H_9F_3O_2$; Formula Weight: 242.19; crystal color, habit: colorless; crystal system: orthorhombic; crystal size: $0.212 \times 0.145 \times 0.089$; lattice parameters: a = 10.2447(19)Å, b = 9.1208(17)Å, c = 23.675(5)Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, V = 2212.2(7)Å³; Space group: *Pbca*; *Z* = 8; $D_{calc} = 1.454$ g/cm³; $F_{000} = 992$; Final *R* indices [*I* > 2sigma(1)]: R1 = 0.0496; wR₂ = 0.1167.
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